Mathematical Formulation for Nonuniform Multiple Dosing

Keyphrases □ Pharmacokinetics—mathematical derivation of nonuniform multiple-dosing equation □ Multiple dosing, nonuniform—mathematical derivation of pharmacokinetic equation

To the Editor:

Consider a three-compartment model with all possible arrows between compartments and an "out" arrow from each compartment. Let k_{ij}, in inverse time units, represent a transfer rate constant from compartment i to compartment j, and let k_{i0} represent the out transfer from compartment i to the outside. Now if x_i is the amount of substance in compartment i, the law of mass action and the hypothesis of simple diffusion lead to the set of differential equations, written in matrix form, where $\dot{x} = dx/dt$:

$$\begin{pmatrix} \dot{x}_1 \\ \dot{x}_2 \\ \dot{x}_3 \end{pmatrix} = \begin{pmatrix} -k_1 & k_{21} & k_{31} \\ k_{12} & -k_2 & k_{32} \\ k_{13} & k_{23} & -k_3 \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \end{pmatrix} \quad \text{(Eq. 1)}$$

Here, $k_1 = k_{10} + k_{12} + k_{13}$, $k_2 = k_{21} + k_{20} + k_{23}$, and $k_3 = k_{31} + k_{32} + k_{30}$.

Let the initial conditions be x_{10}, x_{20}, and x_{30}. Also let the 3 by 3 array of k values of Eq. 1 be represented by capital K, and let bold face denote a vector. Then Eq. 1 can be written as:

$$\mathbf{x} = K\mathbf{x} \quad \text{(Eq. 2)}$$

with initial condition vector $\mathbf{x}_0$.

The structure of the matrix K is evident. There are minus signs on the diagonal elements. The ith diagonal element is the negative sum of all the out arrows from compartment i or, in other words, the negative sum of all k values in column i and the out k from compartment i. Aside from the diagonal elements, the pattern of subscripts in the matrix K is evident. For example, for n compartments, we have:

$$K = \begin{pmatrix} -k_1 & k_{21} & \cdots & k_{n1} \\ k_{12} & -k_2 & \cdots & k_{n2} \\ \cdots & \cdots & & \cdots \\ k_{1n} & k_{2n} & \cdots & -k_n \end{pmatrix} \quad \text{(Eq. 3)}$$

where the diagonal elements are formed as described previously. In the case where some arrows in a particular model are known not to exist, the corresponding k values above are set to zero.

Now consider the use of these differential equations and the equivalent compartmental model to simulate drug transport in pharmacokinetic studies. Suppose that we want to simulate a multiple-dose regimen, where each dose is specified as to the amount of drug given and the time administered.

Niebergall *et al.* (1) stated that "no equation developed to date allows the drug to be administered at varying time intervals." The following development produces such an equation. We must first explain some of the mathematical equipment used. Let $\delta(t - a)$ denote the Dirac delta function, which can be described as a rectangle of infinite height, infinitesimal width, and area 1. More precisely, let:

$$F_w(t - a) = \begin{cases} \frac{1}{w}, a \leq t \leq a + w \\ 0 \text{ otherwise} \end{cases} \quad \text{(Eq. 4)}$$

Then:

$$\lim_{w \to 0} F_w = \delta(t - a) \quad \text{(Eq. 5)}$$

Heaviside's unit step function is defined as:

$$U(t - a) = \begin{cases} 0, t < a \\ 1, t > a \end{cases} \quad \text{(Eq. 6)}$$

which can be described as a step of height 1 located at $t = a$. Standard Laplace transform tables give:

$$L\,\delta(t) = 1 \quad \text{(Eq. 7)}$$

$$L\,\delta(t - a) = \exp(-as) \quad \text{(Eq. 8)}$$

$$LU(t) = 1/s \quad \text{(Eq. 9)}$$

$$LU(t - a) = [\exp(-as)]/s \quad \text{(Eq. 10)}$$

$$LF(t - a)U(t - a) = [\exp(-as)]f(s) \quad \text{(Eq. 11)}$$

Pipes (2) showed that ordinary Laplace transform pairs have their matrix analogs. For example, if a is a scalar:

$$L\exp(at) = (s - a)^{-1} \quad \text{(Eq. 12)}$$

but if A is a square matrix, then:

$$\exp(At) = (I + At + A^2t^2/2! + \ldots) \quad \text{(Eq. 13)}$$

and:

$$L\exp(At) = (sI - A)^{-1} \quad \text{(Eq. 14)}$$

where I is the identity matrix with ones on the diagonal and zeros elsewhere. The superscript denotes matrix inverse.

A simple example will aid in understanding the following mathematical development. Consider a one-compartment open model representing the central or "blood" compartment with an output rate constant k, with one dose injected "instantaneously" at time $t = t_0$ and another dose similarly administered at time $t = t_1$.

The differential equation for this model can be written as:

$$\dot{x} = -kx + \delta(t - t_1) \quad \text{(Eq. 15a)}$$

$$x(0) = x_0 = 1 \quad \text{(Eq. 15b)}$$

Taking the Laplace transform of both sides, we get:

$$sLx - x_0 = -kLx + \exp(-t_1 s) \quad \text{(Eq. 16)}$$

Solving for Lx, we get:

$$Lx = (s + k)^{-1}x_0 + (s + k)^{-1}\exp(-t_1 s) \quad \text{(Eq. 17)}$$

Taking the inverse Laplace transform, we get:

$$x = \exp(-kt)x_0 + \exp[-k(t - t_1)]U(t - t_1) \quad \text{(Eq. 18)}$$

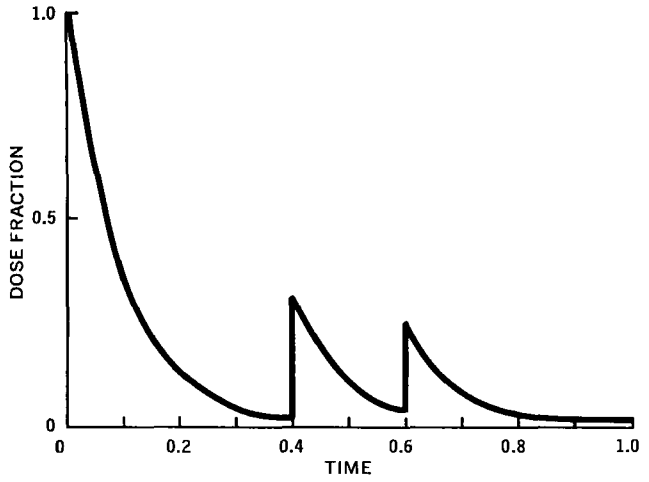


Figure 1—*Dose fraction in Compartment 1 as a function of time.*

This solution can also be written as:

$$x = \exp[-k(t - 0)]U(t - 0) + \exp[-k(t - t_1)]U(t - t_1) \quad \text{(Eq. 19)}$$

which suggests the use of a summation notation for multiple injections.

Consider a three-compartment model as above with multiple-dose amounts a_i at time t_i delivered into Compartment 1. For simplicity, let $i = 1$ and 2, so that the differential equations, in matrix notation, are:

$$\mathbf{x} = K\mathbf{x} + \begin{pmatrix} a_1\delta(t - t_1) + a_2\delta(t - t_2) \\ 0 \\ 0 \end{pmatrix} \quad \text{(Eq. 20)}$$

with a vector $\mathbf{x}_0$ of initial conditions, where δ denotes the Dirac delta function. Taking Laplace transforms, we get:

$$sL\mathbf{x} - \mathbf{x}_0 = KL\mathbf{x} + \begin{pmatrix} a_1 \exp(-t_1 s) \\ 0 \\ 0 \end{pmatrix} + \begin{pmatrix} a_2 \exp(-t_2 s) \\ 0 \\ 0 \end{pmatrix} \quad \text{(Eq. 21)}$$

Collecting terms and solving for $L\mathbf{x}$, we get:

$$L\mathbf{x} = (sI - K)^{-1}\mathbf{x}_0 + (sI - K)^{-1}\begin{pmatrix} a_1 \exp(-t_1 s) \\ 0 \\ 0 \end{pmatrix} + (sI - K)^{-1}\begin{pmatrix} a_2 \exp(-t_2 s) \\ 0 \\ 0 \end{pmatrix} \quad \text{(Eq. 22)}$$

Taking the inverse Laplace transform, we get:

$$\mathbf{x} = \exp(Kt)\mathbf{x}_0 + \exp[K(t - t_1)]\begin{pmatrix} a_1U(t - t_1) \\ 0 \\ 0 \end{pmatrix} + \exp[K(t - t_2)]\begin{pmatrix} a_2U(t - t_2) \\ 0 \\ 0 \end{pmatrix} \quad \text{(Eq. 23)}$$

where U denotes the Heaviside unit step function. When there are n compartments with m multiple doses, we have:

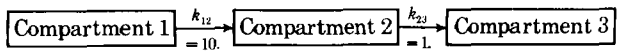
$$\mathbf{x} = \exp(Kt)\mathbf{x}_0 + \sum_{i=1}^{m} \exp[K(t - t_i)]\begin{pmatrix} a_iU(t - t_i) \\ 0 \\ \cdots \\ 0 \end{pmatrix} \quad \text{(Eq. 24)}$$

The matrix exponential function, $\exp(Kt)$, can be calculated directly from its defining expansion given in Eq. 13. Some timesaving shortcuts were given by Pipes and Hovanessian (3).

As an example, let:

$$K = \begin{pmatrix} -10. & 0. & 0. \\ 10. & -1. & 0. \\ 0. & 1. & 0. \end{pmatrix} \qquad \mathbf{x}_0 = \begin{pmatrix} 1. \\ 0. \\ 0. \end{pmatrix} \quad \text{(Eq. 25)}$$

representing Scheme I.



Scheme I

Let $a_1 = .3$, $t_1 = .4$, $a_2 = .2$, and $t_2 = .6$. Calculate $\mathbf{x}$ at $t = 1$ by substituting these values in Eq. 23 to get:

$$\mathbf{x}(1) = \begin{pmatrix} .0000 & .0000 & 0. \\ .4087 & .3679 & 0. \\ .5913 & .6321 & 1. \end{pmatrix}\begin{pmatrix} 1. \\ 0. \\ 0. \end{pmatrix} + \begin{pmatrix} .0025 & .0000 & 0. \\ .6070 & .5488 & 0. \\ .3905 & .4512 & 1. \end{pmatrix}\begin{pmatrix} .3 \\ .0 \\ .0 \end{pmatrix} + \begin{pmatrix} .0183 & .0000 & 0. \\ .7244 & .6703 & 0. \\ .2572 & .3297 & 1. \end{pmatrix}\begin{pmatrix} .2 \\ .0 \\ .0 \end{pmatrix} =$$

$$\begin{pmatrix} .0000 \\ .4087 \\ .5913 \end{pmatrix} + \begin{pmatrix} .0008 \\ .1821 \\ .1172 \end{pmatrix} + \begin{pmatrix} .0037 \\ .1449 \\ .0514 \end{pmatrix} = \begin{pmatrix} .0045 \\ .7357 \\ .7599 \end{pmatrix} \quad \text{(Eq. 26)}$$

where a computer program is used to evaluate the matrix exponential functions by Eq. 13.

To link the solution $\mathbf{x} = \exp(Kt)\mathbf{x}_0$ of Eq. 2 to its solution in terms of scalar exponentials, use known matrix theory (see, for example, Ref. 4).

Let Λ be the diagonal matrix of eigenvalues λ_1, λ_2, . . . , λ_n of K, and let D be a diagonal matrix with diagonal elements $\exp(\lambda_1 t)$, $\exp(\lambda_2 t)$, . . . , $\exp(\lambda_n t)$. Hearon (5) proved that these eigenvalues are all real and nonpositive when Eq. 2 describes a linear com-

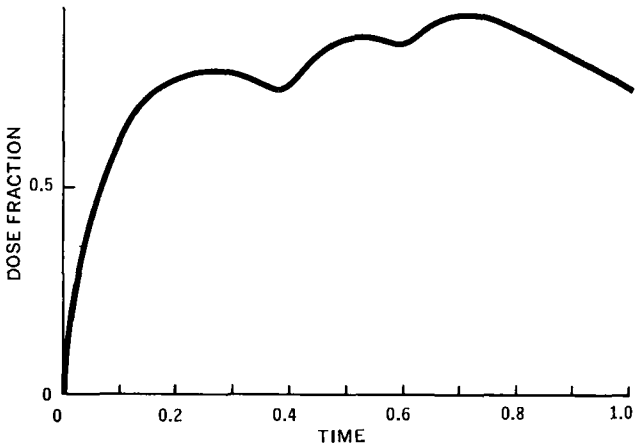


Figure 2—*Dose fraction in Compartment 2 as a function of time.*

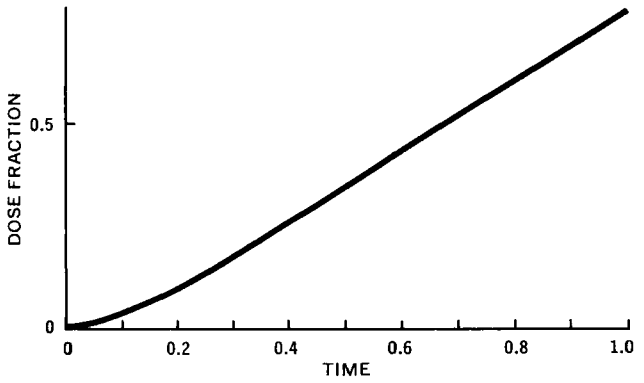


Figure 3—*Dose fraction in Compartment 3 as a function of time.*

partment model, even though K is nonsymmetric. Let $\mathbf{p}_i$ be the real eigenvector of K associated with λ_i, where $P = (\mathbf{p}_1, \mathbf{p}_2, \ldots, \mathbf{p}_n)$ and P^{-1} is the inverse of P. Then the solution of Eq. 2 can be written:

$$\mathbf{x} = PDP^{-1}\mathbf{x}_0 = \sum_{i=1}^{n} b_i \mathbf{p}_i \exp(\lambda_i t) \qquad \text{(Eq. 27)}$$

where $b = P^{-1}\mathbf{x}_0$. Thus, Eq. 24 can be written in terms of scalar exponentials, but the notation is cumbersome.

To evaluate $\mathbf{x}$ for plotting, let $G = \exp(KT)$, where T is a sufficiently small increment of time, say 0.1 in this example. Calculate G once and for all by using Eq. 13 to get:

$$G = \begin{pmatrix} .3679 & .0000 & 0. \\ .5966 & .9048 & 0. \\ .0355 & .0952 & 1. \end{pmatrix} \qquad \text{(Eq. 28)}$$

or by using the eigenvalues of K:

$$\Lambda = \begin{pmatrix} -10. & 0. & 0. \\ 0. & -1. & 0. \\ 0. & 0. & 0. \end{pmatrix} \qquad \text{(Eq. 29)}$$

and the eigenvectors of K:

$$P = \begin{pmatrix} 1.0000 & 0. & 0. \\ -1.1111 & 1. & 0. \\ 0.1111 & -1. & 1. \end{pmatrix} \qquad \text{(Eq. 30)}$$

in Eq. 27. Thus, at time $t = T$, we have:

$$\mathbf{x}(T) = G\mathbf{x}_0 \qquad \text{(Eq. 31)}$$

At $t = 2T$, we have:

$$\mathbf{x}(2T) = G\mathbf{x}(T) \qquad \text{(Eq. 32)}$$

the interpretation being that $\mathbf{x}(T)$ itself is a new set of initial conditions to use in calculating $\mathbf{x}(2T)$. Thus:

$$\mathbf{x}(3T) = G\mathbf{x}(2T) \qquad \text{(Eq. 33)}$$

which gives the values of $\mathbf{x}$ at $t = 0.3$ in the example. Now, similarly calculate $\mathbf{x}(4T)$, which gives the values of $\mathbf{x}$ at $t = 0.4$ but just before the first maintenance dose is given. Now let an asterisk denote the values of $\mathbf{x}$ immediately after the first maintenance dose is given. Then clearly:

$$\mathbf{x}^*(4T) = \mathbf{x}(4T) + (.3, .0, .0)' \qquad \text{(Eq. 34)}$$

where the prime denotes the vector transpose. Then:

$$\mathbf{x}(5T) = G\mathbf{x}^*(4T) \qquad \text{(Eq. 35)}$$

With this approach, it is clear that we can write easily the equations for nonuniform multiple dosing into each compartment, so that in general we have:

$$\mathbf{x}[(n+1)T] = G\mathbf{x}^*(nT) \qquad \text{(Eq. 36)}$$

As a check, we used the Continuous System Modeling Program (6) to integrate Eq. 20 numerically with the arguments of the example. The output plots are shown in Figs. 1–3. Plots of the solution of Eq. 20 can also be obtained by use of an analog computer, provided that one has a multiple-dose generator as described by Howell (7).

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Received April 26, 1974.
Accepted for publication November 29, 1974.

Quantitation, Elimination, and Discussion of Decomposition Product Interference in *N*-Acetyl-*p*-aminophenol Colorimetry

Keyphrases □ *N*-Acetyl-*p*-aminophenol—direct colorimetric analysis, decomposition product interference examined □ Colorimetry—analysis, *N*-acetyl-*p*-aminophenol, degradation product interference examined

To the Editor:

Direct colorimetric assay of *N*-acetyl-*p*-aminophenol (I) has been effected by reaction of I with nitrous acid under mild conditions to form 2-nitro-4-acetamidophenol. This reaction was elucidated by Le Perdriel *et al.* (1), who measured the orange-red color of the phenolate ion; Inamdar and Kaji (2), working separately, assayed using the yellow of the unionized phenol.

Chafetz *et al.* (3) compared these methods with their modified technique employing an entirely aqueous system. Because these methods require only the successive addition of reagents, Daly *et al.* (4) adapted the latter technique to an automated assay apparatus, resulting in excellent recovery data with commercial formulations.

The assay of Le Perdriel *et al.* (1) resulted in good